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Articles

Inhibition of Atherosclerosis Development in Cholesterol-Fed Human Apolipoprotein A-I–Transgenic Rabbits

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Abstract

Background Prospective epidemiological studies support the hypothesis that high levels of high-density lipoprotein (HDL) cholesterol and apolipoprotein (apo) A-I limit atherosclerosis development. However, more data from studies with animal models of atherosclerosis that resemble the human disease are required to demonstrate the effect of apo A-I in the inhibition of atherogenesis. The rabbit is a good animal model for human atherosclerosis.

Methods and Results Human apo A-I–transgenic rabbits have been produced, and we have

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evaluated the effect of apo A-I on the development of atherosclerosis in transgenic rabbits fed a cholesterol-rich diet for 14 weeks. Plasma cholesterol levels of atherogenic apo B-containing lipoproteins were similar for transgenic and control rabbits (>1000 mg/dL), while plasma levels of HDL cholesterol in the transgenic group were always about twice that of the control group (68±11 versus 37±3 mg/dL at 14 weeks; $P<.001$). At the end of the experiment, the amount of aortic surface area covered by lesions as well as the amount of lipid accumulation in the aorta were significantly less in transgenic rabbits compared with the control group (15±12% versus 30±8%, $P<.0027$ for the surface area of the thoracic aorta; 116±31 versus 247±39 μmol/g aorta, $P<.0068$ for cholesterol content in total aorta).

Conclusions Overexpression of human apo A-I in rabbits inhibits the development of atherosclerosis in this animal model that resembles, in many respects, human atherosclerosis.

Key Words: apolipoproteins • atherosclerosis • lipoproteins • cholesterol

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Accumulation of cholesterol in arterial vessel walls is a prominent feature of atherosclerosis.[1] [2] [3] [4] This accumulation results from unbalanced cholesterol influx and efflux in the vessel wall. HDL and its primary apolipoprotein (apo), apo A-I, are the major serum factors considered to mediate reverse cholesterol transport from the blood vessel wall to the liver. Prospective epidemiological studies in humans[5] [6] support the hypothesis that high levels of HDL and apo A-I protect against the progression of atherosclerosis. Badimon et al[7] reported that repeated infusion of human HDL into rabbits fed with cholesterol for 9 weeks resulted in less atherosclerosis compared with controls without HDL infusion. Several studies have shown that overexpression of human apo A-I in specific inbred or genetically engineered strains of mice, natural cholesterol-fed C57BL/6 mice,[8] modified apo E-deficient mice,[9] [10] and transgenic mice that express human apo(a)[11] protects against atherogenesis. However, more data from studies with animal models of atherosclerosis that resemble the human disease are required to demonstrate the precise role of apo A-I in limiting the progression of this disease.

The rabbit has several advantages as an animal model for human atherosclerosis. In rabbits, as in humans, the apo B-containing lipoproteins are the major carriers of cholesterol in plasma.[12] Rabbits, like humans, have cholesteryl ester transfer protein, which plays a central role in the atherosclerotic process.[13] Plasma volumes in rabbits are sufficient to study the metabolism of lipoprotein subclasses and facilitate lipoprotein turnover studies. Furthermore, rabbit atherosclerotic lesions resemble human lesions with respect to the large number of smooth muscle cells, necrotic and acellular lesion cores, extracellular matrix deposition, and occasionally, in older animals, superimposed thrombi.[14] [15] [16] [17] [18] [19] Also, rabbit aortas can provide sufficient material for detailed study of lipid accumulation, such as the quantification of phospholipid

subclasses.[20] Recently, it has been possible to overcome a major problem in the study of atherosclerotic lesions, the difficulty of noninvasively imaging lesions and following their progression. Ultrasound imaging[21] or serial magnetic resonance imaging[22] can detect lesion fine structure, progression, and complications in rabbits. Finally, considerable genetic variation in lipoprotein levels occurs among rabbits, which may mirror the diverse genetic background in humans.

For these reasons, we have produced human apo A-I–transgenic rabbits.[23] Some of these transgenic rabbit lines expressed high plasma levels of human apo A-I and have elevated HDL cholesterol levels. This new model is useful to further examine the function of human apo A-I in lipid metabolism and in atherosclerosis progression. In the present study, we examined the effect of apo A-I in the rabbit model of atherosclerosis and determined that cholesterol-fed human apo A-I–transgenic rabbits were significantly protected from the development of aortic fatty-streak lesions and lipid accumulation.

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Animal Model

New Zealand White rabbits transgenic for human apo A-I (line 20)[23] and nontransgenic littermates (age, 3 months; weight, 3.2±0.5 kg) were housed individually in the Charles River Centre (Saint Aubin les Elbeuf, France). We induced atherosclerosis by feeding the animals a cholesterol-rich diet for 14 weeks (all of the diet [120 g per day] was consumed daily). The amount of cholesterol in the diet was adjusted to produce similar plasma levels of cholesterol carried by atherogenic lipoproteins (VLDL and LDL) for the two groups of rabbits. We prepared the atherogenic diet by spraying normal rabbit chow (NIH-09) with cholesterol.

Plasma Lipid and Apolipoprotein Analysis

After animals had fasted overnight, blood from the animals was collected into a tube that contained 1 mg/mL Na_2 EDTA, 50 mg/L gentamicin sulfate, and 0.1% sodium azide. Plasma was separated by low-speed centrifugation and kept at 4°C until analysis (<1 week). Human apo A-I was quantified by rocket immunoelectrophoresis with rabbit polyclonal antibodies (SEBIA). Total apo A-I was measured by immunonephelometric assay for which five anti-apo A-I monoclonal antibodies (Diagnostics Pasteur Production) were used.[24] Plasma levels of rabbit apo A-I were calculated by subtraction of human apo A-I from total apo A-I. The reproducibility of apo A-I determinations was assessed from quality-control data. The coefficients of variation between apo A-I assays were 5.8% and 7.4% for human and total apo A-I, respectively. Plasma levels of cholesterol and triglycerides were measured by use of commercially available kits (Boehringer Mannheim). HDL cholesterol levels were determined in plasma after precipitation of apo B-containing lipoproteins by polyethylene glycol-6000.

Evaluation of Atherosclerosis

Animals were killed by an overdose of intravenous ketamine (80 mg/kg) and carotid exsanguination. The thoracic aorta from the aortic valves to the diaphragm, above the celiac artery, and the abdominal aorta from the diaphragm to the iliac bifurcation were removed and stripped of adventitial fat and tissue. Then, aortas were cut lengthwise into right and left halves by dorsal and ventral incisions. One half of each aorta was fixed in 10% buffered formalin, and the other half was processed for lipid analysis. The fixed aortas were stained with oil red O to reveal fatty deposits. Morphometric assessment of the percentage of the total aorta covered by lipid deposits was determined by computerized planimetry. For light microscopy observations, segments of the oil red O–stained aortas were embedded in paraffin and then stained with hematoxylin-eosin.

Chemical Analysis of Aortic Wall

Dissected aortas were rinsed in PBS, and the half aortas were extracted with 2:1 (vol/vol) chloroform methanol.[25] The extracted aortic tissues were then lyophilized to obtain a defatted dry weight. Unesterified and esterified cholesterol were determined enzymatically with a fluorometric method.[26] Total phospholipid phosphorus was determined by the Bartlett method.[27]

In Vitro Cellular Cholesterol Efflux

Cellular cholesterol efflux studies with the Fu5AH rat hepatoma cell line incubated with whole sera were performed by use of the system established by de la Llera Moya et al.[28]

Statistical Analysis

All data are expressed as mean±SEM. Plasmatic data have been evaluated by use of ANOVA for repeated measures and the Bonferroni test for differences between groups at each time point. For the other data, the Mann-Whitney test was used to establish significance.

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Plasma Lipids and Apolipoproteins

Eight human apo A-I–transgenic and 15 nontransgenic littermate rabbits were fed a cholesterol-rich diet for 14 weeks. Cholesterol in the diet was initially 0.48 g of cholesterol per 120 g of diet but was later adjusted to produce similar levels of non-HDL cholesterol in the plasma of the two groups of rabbits. Plasma levels of non-HDL cholesterol were evaluated weekly and, after 2 weeks, transgenic and control groups of rabbits consumed 120 g of diet per day supplemented with 0.36 g and 0.48 g of cholesterol, respectively ($P<.0001$), for the remainder of the study. Weight gain was similar on the two diets.

During feeding of these amounts of cholesterol, the levels of non-HDL cholesterol were similar between the two groups (Fig 1) and represented 95% of the total plasma cholesterol. At the same time, the level of HDL cholesterol in the transgenic group (Fig 2) was almost twice the HDL cholesterol level of the control group (68±11 mg/dL versus 37±3 mg/dL for values at 14

weeks; $P<.001$). Cholesterol distribution between VLDL and LDL was similar for the two groups. Endogenous rabbit apo A-I and human apo A-I plasma levels during the experiment were determined in the two groups (Fig 3). The total (human plus rabbit) apo A-I plasma level was threefold higher in the transgenic group compared with the control group. The variation in level of total apo A-I over time in response to the cholesterol diet was similar between transgenic and control rabbits (Fig 3A). In transgenic rabbits, at the beginning of the diet, human apo A-I decreased rapidly while rabbit apo A-I increased (Fig 3B). A similar inverse variation of rabbit and human apo A-I was observed previously in transgenic rabbits.[23] When data from the two groups were pooled, the HDL cholesterol levels correlated with total apo A-I levels ($P<.0005$). For the transgenic group, HDL cholesterol levels (week 14) correlated with total apo A-I ($P<.0017$) and human apo A-I ($P<.0018$) levels.

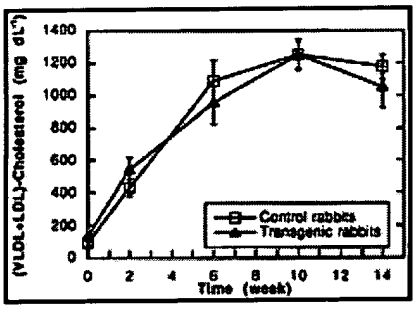

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Figure 1. Cholesterol plasma levels of apolipoprotein B-containing lipoproteins (VLDL+LDL) during feeding of the cholesterol-supplemented diet. Values are expressed as milligram per deciliter. There were no statistical differences between the VLDL+LDL plasma cholesterol levels in the transgenic (n=8) and control (n=15) groups (no group effect; no interaction between groups and times; time effect, $P<.001$, but no differences between the two groups for each time point).

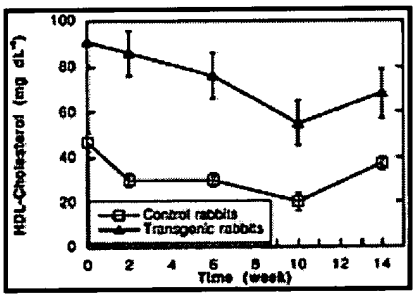

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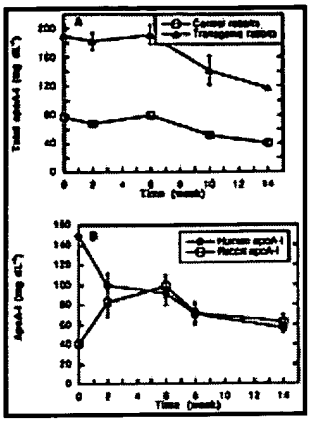
Figure 2. Cholesterol plasma levels of the HDL fraction during the diet. Values are expressed as milligram per deciliter. HDL cholesterol values were twofold to threefold higher in the transgenic (n=8) group than in the control (n=15) group (group and time effect, $P<.001$ and $P<.001$, respectively; $P<.001$ for differences between the two groups at each time point).

Figure 3. Apolipoprotein A-I (apoA-I) plasma levels during the diet. Values are expressed as milligram per deciliter. A, Plasma levels of total apoA-I for control (n=15) and transgenic (n=8) rabbits (group and time effect, $P<.001$ and $P<.001$, respectively; significant differences between the two groups for



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each time point, $P<.001$). B, Endogenous rabbit and human plasma levels of apoA-I for transgenic rabbits (n=8; $P<.001$ for differences between groups at baseline; no differences at other time points).

Morphological and Histological Analysis

Thoracic and abdominal aortas were stained with oil red O. The control group had 30±8% of the thoracic aorta surface covered by lesions, whereas only 15±12% (50% of control; $P<.0027$) of the thoracic aorta surface of transgenic rabbits was covered by lesions (Fig 4). Similar results were observed for the abdominal aortas. Histological examination of the aortas of the two groups of rabbits revealed similar lesions characterized by a large accumulation of macrophage foam cells and some smooth muscle cells in the intima.

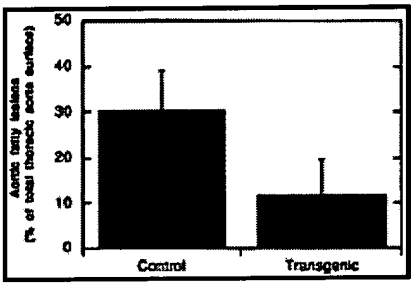

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Figure 4. Atherosclerosis involvement in thoracic aorta. Values are expressed as percent of aortic surface covered by fatty streaks ($P<.0027$, transgenic [n=8] vs control [n=15] groups).

Lipid Accumulation in the Aortic Wall

To analyze lipid accumulation, a chemical analysis of the lipids extracted from the aortic wall was performed. The amount of total cholesterol per gram of defatted dry weight of total aorta in the transgenic group (Fig 5) was 47% that of the control group (116±31 versus 247±39 μmol/g aorta; $P<.0068$). This reflected a reduced accumulation of cholesteryl ester in the transgenic group that was 38% the level of the control group (66±22 versus 172±29 μmol/g aorta; $P<.0023$) as well as a lower accumulation of unesterified cholesterol in the transgenic group that was 64%

the level of the control group (48±9 versus 74±9 μmol/g aorta; $P<.05$). The cholesteryl ester content in the total aorta corresponded to 67.3±1.5% of total cholesterol for the control group and 46.7±6.8% of total cholesterol for the transgenic group (69% of control; $P<.0001$). In addition, the phospholipid accumulation per gram of defatted dry weight of total aorta was also reduced in the transgenic group, to 80% of control (39±2 versus 49±3 μmol/g aorta; $P<.0225$).

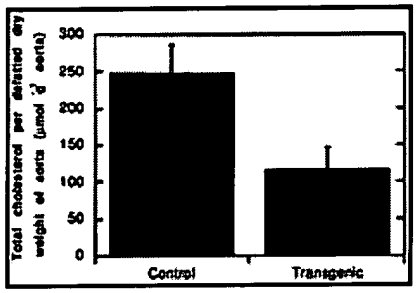

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Figure 5. Total cholesterol accumulation in entire aorta. Values are expressed as micromoles per gram of defatted dry weight of total aorta ($P<.0068$, transgenic [n=8] vs control [n=15] groups).

Cellular Cholesterol Efflux

To determine the potential mechanism of atherosclerosis protection in transgenic rabbits, the efflux of labeled cholesterol from Fu5AH cells exposed to 5% diluted serum from transgenic and control rabbits (after 14 weeks of atherogenic diet) was determined. All serum samples promoted cholesterol efflux. However, mean cholesterol efflux promoted by the incubation of serum samples from the transgenic group (Fig 6) was significantly higher than that from the control group (+24.5% of control value at 2 hours and +20.2% of control value at 4 hours; $P<.0001$). The relationships between cholesterol efflux and non-HDL cholesterol levels, HDL cholesterol levels, and concentration of total or human apo A-I levels were analyzed. No correlation was found between cholesterol efflux and non-HDL cholesterol. When data from the two groups were pooled, cholesterol efflux correlated with total apo A-I levels at 2 ($P<.0005$; Fig 7) and 4 hours ($P<.013$) of incubation and with HDL cholesterol levels at 2 ($P<.01$) and 4 hours ($P<.05$) of incubation. For the transgenic group, cholesterol efflux correlated with total apo A-I levels at 2 hours ($P<.043$).

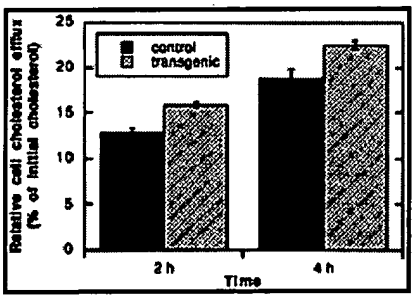

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Figure 6. Relative cholesterol efflux. Serum from transgenic and control rabbits was incubated with cholesterol-enriched Fu5AH cells, and cholesterol efflux by the cells was measured after 2 and 4 hours of incubation at 37°C. Values are expressed as percent of initial cholesterol present in the cells that was found in the medium after incubation. Values are the mean of relative cholesterol efflux promoted by the incubation of serum from control (n=15) or transgenic (n=8) rabbits.

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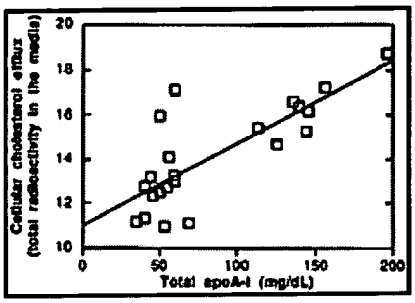

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Figure 7. Relation between cellular cholesterol efflux and total apolipoprotein A-I (apo A-I) plasma levels for transgenic (n=8) and control (n=15) rabbits. Cellular cholesterol efflux at 2 hours was highly correlated with total apo A-I plasma levels (r=.806, P<.0005).

Discussion

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Our results demonstrate the protective effect of apo A-I in an animal model of atherosclerosis that resembles human atherosclerosis in many respects. We found that overexpression of human apo A-I in cholesterol-fed transgenic rabbits significantly inhibited the development of aortic fatty-streak lesions and lipid accumulation. In addition, at least one mechanism by which apo A-I and HDL may act to prevent atherosclerosis progression in this model was suggested from the results: enhancement of reverse cholesterol transport.

Surprisingly, in a preliminary experiment, we observed that transgenic animals developed a higher degree of hypercholesterolemia than control rabbits in response to 1% (wt/wt) cholesterol in their diet. The higher degree of hypercholesterolemia in transgenic rabbits was compatible with an inhibition of hepatic lipase by apo A-I as described previously.[29] [30] [31] [32] Transgenic rabbits fed an unsupplemented chow diet showed cholesterol levels of atherogenic lipoproteins similar to levels in transgenic rabbits.[23] Hepatic lipase activity varies widely between species. It is high in humans and rats and very low in rabbits (15% of human hepatic lipase activity).[32] [33] [34] Therefore, enhancement of hypercholesterolemia in the apo A-I–transgenic rabbits may reflect the combined effect of high plasma levels of human apo A-I and low levels of hepatic lipase in rabbits. To evaluate the effect of the apo A-I transgene on atherosclerosis development, it was necessary to adjust the level of cholesterol in the diet to produce the same level of non-HDL cholesterol in the plasma of the transgenic and nontransgenic groups of rabbits. Such a technique was used previously to reduce variation in groups of animals in which large genetic diversity occurs. In view of the prospect of human gene therapy for atherosclerotic vascular disease by production of high plasma levels of apo A-I, it will be important to assess further the mechanism

of apo A-I–induced hypercholesterolemia.

Dramatic inhibition of diet-induced atheroma was demonstrated in the apo A-I–transgenic rabbits. Lipid accumulation and lesion area were reduced ≈50% in the aortas of transgenic rabbits compared with control rabbits. Many factors have been proposed as important for the development of atherosclerotic lesions. The results of the present study suggest that apo A-I is very effective in correcting the imbalance of factors that determine the rate of atherogenesis. Because there were no differences in plasma cholesterol levels in the fractions of apo B-containing lipoproteins between the two groups of rabbits, the effect of the human apo A-I transgene on atherosclerosis must be related to the higher levels of HDL cholesterol and apo A-I in the plasma of the transgenic animals.

An abundance of data that confirm the inverse relation between HDL and atherosclerotic vascular disease has been reported.[5,6] Studies in culture systems[35,36] supported the hypothesis that apo A-I–containing lipoproteins exert a beneficial effect against development of atherosclerosis. Such studies indicated that HDL facilitates reverse cholesterol transport, during which cholesterol is transported away from cells of extrahepatic tissues and carried back to the liver, where it can be eliminated or reused. Although other mechanisms have been proposed for the antiatherosclerotic effect of HDL, the present in vitro cellular cholesterol efflux studies strongly support the hypothesis that HDL-rich plasma stimulates reverse cholesterol transport. The Fu5AH cell culture system was previously used to evaluate the potential of sera to promote cellular cholesterol efflux.[24] In agreement with the data reported with human sera, there was no correlation between cholesterol efflux and the content of apo B-containing lipoproteins in serum samples. Although apo B-containing lipoproteins can enrich Fu5AH cells with cholesterol, these lipoproteins do not appear to affect the rate of removal of cholesterol from Fu5AH cells. On the other hand, the highest correlation with cholesterol efflux was found with HDL cholesterol and total apo A-I plasma levels. Moreover, cholesterol efflux was higher when Fu5AH cells were incubated with sera from transgenic versus control rabbits. In a report that described the human apo A-I–transgenic rabbit line,[23] we described the presence of a large amount of apo A-I–containing lipoproteins with pre-ß mobility. These particles are considered the primary acceptor of cholesterol efflux from the plasma membrane,[37] and their plasma levels were correlated with cholesterol efflux.[23] HDL promotes cholesterol efflux from cholesterol-enriched human monocyte-derived macrophages[38] and also limits cholesterol accumulation in these cells during cholesterol enrichment. Therefore, it is likely that HDL can limit cholesterol accumulation in cells even as these cells are accumulating cholesterol.

The present study demonstrated that human apo A-I produced in the liver of transgenic rabbits enhanced reverse cholesterol transport and protected the aorta from diet-induced atherosclerosis, despite similar levels of atherogenic lipoproteins in the plasma of the transgenic and control rabbits. The rabbit is a good animal model for human atherosclerosis and is well suited for many types of studies. The data generated from this model will enhance our understanding of the role of apo A-I in protecting against the development of atherosclerosis.

Acknowledgments

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1. Buck RC, Rossiter RJ. Lipids of normal and atherosclerotic aortas. *Arch Pathol.* 1951;51:224-237.
2. Bottcher CJF, Woodford FP. Chemical changes in the arterial wall associated with atherosclerosis. *Fed Proc.* 1962;21(suppl 11):11-19.
3. Insull W Jr, Bartoch GE. Cholesterol, triglyceride, and phospholipid content of the intima, media and atherosclerotic fatty streak in human thoracic aorta. *J Clin Invest.* 1966;45:513-523.[Medline] [Order article via Infotrieve]
4. Katz SS, Shipley GG, Small DM. Physical chemistry of the lipids of human atherosclerosis lesions: demonstration of a lesion intermediate between fatty streaks and advanced plaques. *J Clin Invest.* 1976;58:200-211.[Medline] [Order article via Infotrieve]
5. Gordon DJ, Knoke J, Probsfield JL, Superko R, Tyroler HA. High-density lipoprotein cholesterol and coronary heart disease in hypercholesterolemic men: the Lipid Research Clinics Coronary Primary Prevention Trial. *Circulation.* 1986;74:1217-1225.[Abstract]
6. Miller NE. Associations of high-density lipoprotein subclasses and apolipoproteins with ischemic heart disease and coronary atherosclerosis. *Am Heart J.* 1987;113:589-597. [Medline] [Order article via Infotrieve]
7. Badimon JJ, Badimon L, Fuster V. Regression of atherosclerotic lesions by high density lipoprotein plasma fraction in the cholesterol-fed rabbit. *J Clin Invest.* 1990;85:1234-1241. [Medline] [Order article via Infotrieve]
8. Rubin EM, Krauss RM, Spangier EA, Verstuyft JG, Gift SM. Inhibition of early atherogenesis in transgenic mice by human apolipoprotein AI. *Nature.* 1991;353:265-267. [Medline] [Order article via Infotrieve]
9. Paszty C, Maeda N, Verstuyft J, Rubin EM. Apolipoprotein Al transgene corrects apolipoprotein E deficiency-induced atherosclerosis in mice. *J Clin Invest.* 1994;94:899-903.[Medline] [Order article via Infotrieve]
10. Plump AS, Scott CJ, Breslow JL. Human apolipoprotein A-I gene expression increases high density lipoprotein and suppresses atherosclerosis in the apolipoprotein E-deficient mouse. *Proc Natl Acad Sci U S A.* 1994;91:9607-9611.[Abstract/Free Full Text]
11. Liu AC, Lawn RM, Verstuyft JG, Rubin EM. Human apolipoprotein A-I prevents atherosclerosis associated with apolipoprotein[a] in transgenic mice. *J Lipid Res.* 1994;35:2263-2267.[Abstract]
12. Chapman JM. Comparative analysis of mammalian plasma lipoproteins. *Methods Enzymol.* 1986;128:71-147.
13. Nagashima M, McLean JW, Lawn RL. Cloning and mRNA tissue distribution of rabbit cholesteryl ester transfer protein. *J Lipid Res.* 1988;29:1643-1649.[Abstract]

14. Bocan TMA, Bak Mueller S, Uhlendorf PD, Newton RS, Krause BR. Comparison of CI-976, an ACAT inhibitor, and selected lipid-lowering agents for antiatherosclerotic activity in iliac-femoral and thoracic aortic lesions: a biochemical, morphological, and morphometric evaluation. *Arterioscler Thromb.* 1991;11:1830-1843.[Abstract]
15. Tsukada T, Rosenfeld M, Ross R, Gow AM. Immunocytochemical analysis of cellular components in atherosclerotic lesions: use of monoclonal antibodies with the Watanabe and fat-fed rabbit. *Arteriosclerosis.* 1986;6:601-613.[Abstract]
16. Adams CMV, Miller NE, Morgan RS, Rao SN. Lipoprotein levels and tissue lipids in fatty-fibrous atherosclerosis induced in rabbits by two years' cholesterol feeding at a low level. *Atherosclerosis.* 1982;44:1-8.[Medline] [Order article via Infotrieve]
17. Lupu F, Danaricu I, Simionescu N. Development of intracellular lipid deposits in the lipid-laden cells of atherosclerotic lesions: a cytochemical and ultrastructural study. *Atherosclerosis.* 1987;67:127-142.[Medline] [Order article via Infotrieve]
18. Hunt CE, Duncan LA. Hyperlipoproteinaemia and atherosclerosis in rabbits fed low-level cholesterol and lecithin. *Br J Exp Pathol.* 1985;66:35-46.[Medline] [Order article via Infotrieve]
19. Davies MJ. A critical analysis of animal models of atherosclerosis and restenosis. In: Conference proceedings of the Bristol-Myers Squibb Symposium on Cardiovascular Research, volume 10; 1993; Seattle, Wash. Abstract 1.
20. Chao FF, Blanchette-Mackie EJ, Dickens BJ, Gamble W, Kruth HS. Development of unesterified cholesterol rich lipid particles in ath-erosclerotic lesions of WHHL and cholesterol-fed rabbits. *J Lipid Res.* 1994;35:71-83.[Abstract]
21. Blankenhorn DH, Selzer RH, Crawford DW, Barth JB, Liu CR, Liu CH, Mack WJ, Alaupovic P. Beneficial effects of colestipol-niacin therapy on the common carotid artery: 2-year and 4-year reduction of intima-media thickness measured by ultrasound. *Circulation.* 1993;88:20-28.[Abstract]
22. Skinner MP, Yuan C, Mitsumori L, Hayes CE, Raines EW, Nelson JA, Ross R. Serial magnetic resonance imaging of experimental atherosclerosis detects lesion fine structure, progression and complications in vivo. *Nat Med.* 1995;1:69-73.[Medline] [Order article via Infotrieve]
23. Duverger N, Viglietta C, Berthou L, Emmanuel F, Tailleux A, Parmentier-Nihoul L, Laine B, Fievet C, Castro G, Fruchart JC, Houdebine LM, Denefle P. Transgenic rabbits expressing human apolipoprotein A-I in the liver. *Arterioscler Thromb Vasc Biol.* In press.
24. Pruvost I, Fievet C, Durieux C, Vu Dac N, Fruchart JC. Electroimmuno- and immunonephelometric assays of apolipoprotein A-I by using a mixture of monoclonal antibodies. *Clin Chem.* 1988;34:2048-2052.[Abstract/Free Full Text]
25. Floch J, Lees M, Sloane Stanley GH. A simple method for the isolation and purification of total lipids from animals tissues. *J Biol Chem.* 1957;226:497-509.[Free Full Text]
26. Gamble W, Vaughan M, Kruth HS, Avigan J. Procedure for determination of free and total cholesterol in micro- or nanogram amounts suitable for studies with cultured cells. *J Lipid Res.* 1978;19:1068-1070.[Abstract]
27. Bartlett GR. Phosphorus assay in column chromatography. *J Biol Chem.* 1959;234:466-468.[Free Full Text]
28. de la Llera Moya M, Atger V, Paul JL, Fournier N, Moatti N, Giral P, Friday KE, Rothblat G. A cell culture system for screening human serum ability to promote cellular cholesterol efflux. *Arterioscler Thromb.* 1994;14:1056-1065.[Abstract]
29. Kubo M, Matsuzawa Y, Tajima S, Ishikawa K, Yamamoto A, Tarui S. ApoA-I and apoA-II inhibit hepatic triglyceride lipase from post human heparin plasma. *Biochem Biophys Res Commun.* 1981;100:261-266.[Medline] [Order article via Infotrieve]
30. Zhong S, Golberg IJ, Bruce C, Rubin E, Breslow JL, Tall A. Human apoA-II inhibits the hydrolysis of HDL triglyceride and the decrease of HDL size induced by

hypertriglyceridemia and cholesteryl ester transfer protein in transgenic mice. *J Clin Invest.* 1994;94:2457-2467.[Medline] [Order article via Infotrieve]

31. Shinomiya M, Sasaki M, Barnhart RL, Shirai K, Jackson RL. Effect of apolipoproteins on the hepatic lipase catalyzed hydrolysis of human plasma high density lipoprotein$_2$-triacylglycerols. *Biochim Biophys Acta.* 1982;713:292-299.[Medline] [Order article via Infotrieve]
32. Clay MA, Hopkins GJ, Ehnholm CP, Barter PJ. The rabbit as an animal model of hepatic lipase deficiency. *Biochim Biophys Acta.* 1989;1002:173-181.[Medline] [Order article via Infotrieve]
33. Newnham HH, Hopkins GJ, Devlin S, Barter PJ. Lipoprotein lipase prevents the hepatic lipase-induced reduction in particle size of high density lipoproteins during incubation of human plasma. *Atherosclerosis.* 1990;82:167-176.[Medline] [Order article via Infotrieve]
34. Olivecrona T, Bengtsson-Olivecrona G. Lipoprotein lipase and hepatic lipase. *Curr Opin Lipidol.* 1993;4:187-196.
35. Rothblat GH, Mahlberg FH, Johnson WJ, Phillips MC. Apolipoproteins, membrane cholesterol domains, and the regulation of cholesterol efflux. *J Lipid Res.* 1992;33:1091-1097.[Abstract]
36. Fielding CJ, Fielding PE. Molecular physiology of reverse cholesterol transport. *J Lipid Res.* 1995;36:211-228.[Abstract]
37. Castro GR, Fielding CJ. Early incorporation of cell-derived cholesterol into prebeta-migrating high density lipoprotein. *Biochemistry.* 1988;25:25-29.
38. Skarlatos SI, Duverger N, Rader D, Kruth HS. Cholesterol efflux from human monocyte-derived macrophages in the presence of LpA-I:A-II. *Biochim Biophys Acta.* 1995;1270:19-25.[Medline] [Order article via Infotrieve]

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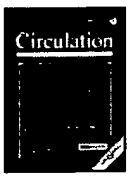


Differential Effects of Apolipoprotein A-I-Mimetic Peptide on Evolving and Established Atherosclerosis in Apolipoprotein E-Null Mice
Circulation, September 21, 2004; 110(12): 1701 - 1705.
[Abstract] [Full Text] [PDF]

Arteriosclerosis, Thrombosis, and Vascular Biology ▸HOME

D. L. Macdonald, T. L. Terry, L. B. Agellon, P. N. Nation, and G. A. Francis
Administration of Tyrosyl Radical-Oxidized HDL Inhibits the Development of Atherosclerosis in Apolipoprotein E-Deficient Mice
Arterioscler. Thromb. Vasc. Biol., September 1, 2003; 23(9): 1583 - 1588.
[Abstract] [Full Text] [PDF]

Circulation ▸HOME

Y. Zhang, I. Zanotti, M. P. Reilly, J. M. Glick, G. H. Rothblat, and D. J. Rader
Overexpression of Apolipoprotein A-I Promotes Reverse Transport of Cholesterol From Macrophages to Feces In Vivo
Circulation, August 12, 2003; 108(6): 661 - 663.
[Abstract] [Full Text] [PDF]

Circulation ▸HOME

L. M. Belalcazar, A. Merched, B. Carr, K. Oka, K.-H. Chen, L. Pastore, A. Beaudet, and L. Chan
Long-Term Stable Expression of Human Apolipoprotein A-I Mediated by Helper-Dependent Adenovirus Gene Transfer Inhibits Atherosclerosis Progression and Remodels Atherosclerotic Plaques in a Mouse Model of Familial Hypercholesterolemia
Circulation, June 3, 2003; 107(21): 2726 - 2732.
[Abstract] [Full Text] [PDF]

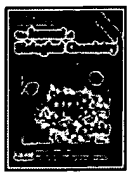
Circulation ▸HOME

J. X. Rong, J. Li, E. D. Reis, R. P. Choudhury, H. M. Dansky, V. I. Elmalem, J. T. Fallon, J. L. Breslow, and E. A. Fisher
Elevating High-Density Lipoprotein Cholesterol in Apolipoprotein E-Deficient Mice Remodels Advanced Atherosclerotic Lesions by Decreasing Macrophage and Increasing Smooth Muscle Cell Content
Circulation, November 13, 2001; 104(20): 2447 - 2452.
[Abstract] [Full Text] [PDF]

Circulation ▸HOME

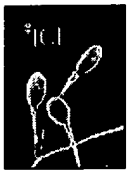
P. K. Shah, S. Kaul, J. Nilsson, and B. Cercek
Exploiting the Vascular Protective Effects of High-Density Lipoprotein and Its Apolipoproteins: An Idea Whose Time for Testing Is Coming, Part I
Circulation, November 6, 2001; 104(19): 2376 - 2383.

[Full Text] [PDF]



JBC Online ▸HOME

H. Ishiguro, H. Yoshida, A. S. Major, T. Zhu, V. R. Babaev, M. F. Linton, and S. Fazio
Retrovirus-mediated Expression of Apolipoprotein A-I in the Macrophage Protects against Atherosclerosis in Vivo
J. Biol. Chem., September 28, 2001; 276(39): 36742 - 36748.
[Abstract] [Full Text] [PDF]

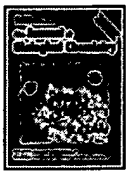


Journal of Clinical Investigation ▸HOME

G. Martin, H. Duez, C. Blanquart, V. Berezowski, P. Poulain, J.-C. Fruchart, J. Najib-Fruchart, C. Glineur, and B. Staels
Statin-induced inhibition of the Rho-signaling pathway activates PPAR{{alpha}} and induces HDL apoA-I
J. Clin. Invest., June 1, 2001; 107(11): 1423 - 1432.
[Abstract] [Full Text] [PDF]

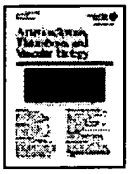
JOURNAL OF LIPID RESEARCH ▸HOME

L. Calabresi, G. Tedeschi, C. Treu, S. Ronchi, D. Galbiati, S. Airoldi, C. R. Sirtori, Y. Marcel, and G. Franceschini
Limited proteolysis of a disulfide-linked apoA-I dimer in reconstituted HDL
J. Lipid Res., June 1, 2001; 42(6): 935 - 942.
[Abstract] [Full Text]



JBC Online ▸HOME

G. Lambert, N. Sakai, B. L. Vaisman, E. B. Neufeld, B. Marteyn, C.-C. Chan, B. Paigen, E. Lupia, A. Thomas, L. J. Striker, J. Blanchette-Mackie, G. Csako, J. N. Brady, R. Costello, G. E. Striker, A. T. Remaley, H. B. Brewer Jr., and S. Santamarina-Fojo
Analysis of Glomerulosclerosis and Atherosclerosis in Lecithin Cholesterol Acyltransferase-deficient Mice
J. Biol. Chem., April 27, 2001; 276(18): 15090 - 15098.
[Abstract] [Full Text] [PDF]



Arteriosclerosis, Thrombosis, and Vascular Biology ▸HOME

P. N. Durrington, B. Mackness, and M. I. Mackness
Paraoxonase and Atherosclerosis
Arterioscler. Thromb. Vasc. Biol., April 1, 2001; 21(4): 473 - 480.
[Abstract] [Full Text] [PDF]

JVIR ▸HOME

M. Narayanaswamy, K. C. Wright, and K. Kandarpa
Animal Models for Atherosclerosis, Restenosis, and Endovascular Graft Research
J. Vasc. Interv. Radiol., January 1, 2000; 11(1): 5 - 17.

[Full Text]

Arteriosclerosis, Thrombosis, and Vascular Biology HOME

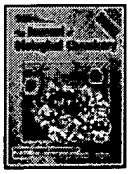
A. von Eckardstein, J.-R. Nofer, and G. Assmann
High Density Lipoproteins and Arteriosclerosis : Role of Cholesterol Efflux and Reverse Cholesterol Transport
Arterioscler. Thromb. Vasc. Biol., January 1, 2001; 21(1): 13 - 27.
[Abstract] [Full Text] [PDF]

Arteriosclerosis, Thrombosis, and Vascular Biology HOME

Bart De Geest, D. Stengel, M. Landeloos, M. Lox, L. Le Gat, D. Collen, P. Holvoet, and E. Ninio
Effect of Overexpression of Human Apo A-I in C57BL/6 and C57BL/6 Apo E-Deficient Mice on 2 Lipoprotein-Associated Enzymes, Platelet-Activating Factor Acetylhydrolase and Paraoxonase : Comparison of Adenovirus-Mediated Human Apo A-I Gene Transfer and Human Apo A-I Transgenesis
Arterioscler. Thromb. Vasc. Biol., October 1, 2000; 20(10): e68 - 75.
[Abstract] [Full Text] [PDF]

Circulation HOME

P. Benoit, F. Emmanuel, J. M. Caillaud, L. Bassinet, G. Castro, P. Gallix, J. C. Fruchart, D. Branellec, P. Denefle, and N. Duverger
Somatic Gene Transfer of Human ApoA-I Inhibits Atherosclerosis Progression in Mouse Models
Circulation, January 12, 1999; 99(1): 105 - 110.
[Abstract] [Full Text] [PDF]



JBC Online HOME

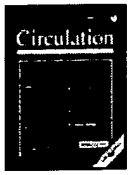
B. Foger, M. Chase, M. J. Amar, B. L. Vaisman, R. D. Shamburek, B. Paigen, J. Fruchart-Najib, J. A. Paiz, C. A. Koch, R. F. Hoyt, H. B. Brewer Jr., and S. Santamarina-Fojo
Cholesteryl Ester Transfer Protein Corrects Dysfunctional High Density Lipoproteins and Reduces Aortic Atherosclerosis in Lecithin Cholesterol Acyltransferase Transgenic Mice
J. Biol. Chem., December 24, 1999; 274(52): 36912 - 36920.
[Abstract] [Full Text] [PDF]

Circulation HOME

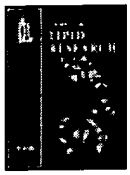
H. M. Dansky and E. A. Fisher
High-Density Lipoprotein and Plaque Regression : The Good Cholesterol Gets Even Better
Circulation, October 26, 1999; 100(17): 1762 - 1763.
[Full Text] [PDF]

Circulation HOME

R. K. Tangirala, K. Tsukamoto, S. H. Chun, D. Usher, E. Pure, and D. J.



Rader
Regression of Atherosclerosis Induced by Liver-Directed Gene Transfer of Apolipoprotein A-I in Mice
Circulation, October 26, 1999; 100(17): 1816 - 1822.
[Abstract] [Full Text] [PDF]



JOURNAL OF LIPID RESEARCH ▸HOME

G. Lambert, M. B. Chase, K. Dugi, A. Bensadoun, H. B. Brewer , Jr., and S. Santamarina-Fojo
Hepatic lipase promotes the selective uptake of high density lipoprotein-cholesteryl esters via the scavenger receptor B1
J. Lipid Res., July 1, 1999; 40(7): 1294 - 1303.
[Abstract] [Full Text]

Arteriosclerosis, Thrombosis, and Vascular Biology ▸HOME

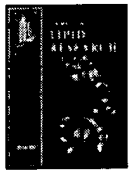
W. A. Boisvert, A. S. Black, and L. K. Curtiss
ApoA1 Reduces Free Cholesterol Accumulation in Atherosclerotic Lesions of ApoE–Deficient Mice Transplanted With ApoE–Expressing Macrophages
Arterioscler. Thromb. Vasc. Biol., March 1, 1999; 19(3): 525 - 530.
[Abstract] [Full Text] [PDF]

JOURNAL OF LIPID RESEARCH ▸HOME

M. E. Brousseau and J. M. Hoeg
Transgenic rabbits as models for atherosclerosis research
J. Lipid Res., March 1, 1999; 40(3): 365 - 375.
[Abstract] [Full Text]

Arteriosclerosis, Thrombosis, and Vascular Biology ▸HOME

A. Matsunaga, J. Sasaki, H. Han, W. Huang, M. Kugi, T. Koga, S. Ichiki, T. Shinkawa, and K. Arakawa
Compound Heterozygosity for an Apolipoprotein A1 Gene Promoter Mutation and a Structural Nonsense Mutation With Apolipoprotein A1 Deficiency
Arterioscler. Thromb. Vasc. Biol., February 1, 1999; 19(2): 348 - 355.
[Abstract] [Full Text] [PDF]

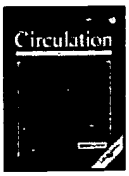


JOURNAL OF LIPID RESEARCH ▸HOME

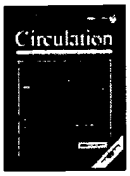
P. W. Baker, K.-A. Rye, J. R. Gamble, M. A. Vadas, and P. J. Barter
Ability of reconstituted high density lipoproteins to inhibit cytokine-induced expression of vascular cell adhesion molecule-1 in human umbilical vein endothelial cells
J. Lipid Res., February 1, 1999; 40(2): 345 - 353.
[Abstract] [Full Text]

Circulation ▸HOME

A. Mamontova, S. Seguret-Mace, B. Esposito, C. Chaniale, M. Bouly, N.



Delhaye-Bouchaud, G. Luc, B. Staels, N. Duverger, J. Mariani, and A. Tedgui
Severe Atherosclerosis and Hypoalphalipoproteinemia in the Staggerer Mouse, a Mutant of the Nuclear Receptor ROR{alpha}
Circulation, December 15, 1998; 98(24): 2738 - 2743.
[Abstract] [Full Text] [PDF]

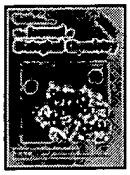


Circulation ▸HOME

B. De Geest, Z. Zhao, D. Collen, and P. Holvoet
Effects of Adenovirus-Mediated Human Apo A-I Gene Transfer on Neointima Formation After Endothelial Denudation in Apo E–Deficient Mice
Circulation, December 16, 1997; 96(12): 4349 - 4356.
[Abstract] [Full Text]

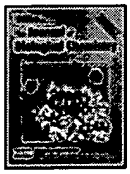
Proceedings of the National Academy of Sciences ▸HOME

O. Stein, Y. Dabach, G. Hollander, M. Ben-Naim, G. Halperin, J. L. Breslow, and Y. Stein
Delayed loss of cholesterol from a localized lipoprotein depot in apolipoprotein A-I-deficient mice
PNAS, September 2, 1997; 94(18): 9820 - 9824.
[Abstract] [Full Text] [PDF]



JBC Online ▸HOME

N. Vu-Dac, P. Gervois, T. Grotzinger, P. De Vos, K. Schoonjans, J.-C. Fruchart, J. Auwerx, J. Mariani, A. Tedgui, and B. Staels
Transcriptional Regulation of Apolipoprotein A-I Gene Expression by the Nuclear Receptor RORalpha
J. Biol. Chem., September 5, 1997; 272(36): 22401 - 22404.
[Abstract] [Full Text] [PDF]



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Y. Huang, S. W. Schwendner, S. C. Rall Jr., D. A. Sanan, and R. W. Mahley
Apolipoprotein E2 Transgenic Rabbits. MODULATION OF THE TYPE III HYPERLIPOPROTEINEMIC PHENOTYPE BY ESTROGEN AND OCCURRENCE OF SPONTANEOUS ATHEROSCLEROSIS
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